U.S. FOOD & DRUG ADMINISTRATION

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Pharmacovigilance (DPV)

PHARMACOVIGILANCE PLAN (PVP) ORIGINAL BLA MEMORANDUM

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To: Zuben Sauna, PhD
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Subject: Pharmacovigilance Plan Review Memorandum

Sponsor: Bioverativ (a Sanofi company)

Product: ALTUVIIIO™ (recombinant antihemophilic, FC-von Willebrand factor-XTEN fusion protein)

Application Number: BLA 125771

Proposed Indication: Treatment of adults and children with hemophilia A (congenital Factor VIII deficiency) for:
(1) Routine prophylaxis to reduce the frequency of bleeding episodes;
(2) On-demand treatment and control of bleeding episodes;
(3) Perioperative management of bleeding.

Submission date: 6/30/2022

Action Due Date: 2/28/2023

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA STN125771/0 based on the safety profile of ALTUVIIIO. The review will determine whether any additional pharmacovigilance actions, such as safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) are warranted, or if Risk Evaluation and Mitigation Strategies (REMS) are required for ALTUVIIIO, should the indication for this product be approved. Please refer to the Appendix for the complete list of materials reviewed for this memorandum.

2 BACKGROUND

Hemophilia A is an X-chromosome linked bleeding disorder that occurs predominantly in males and is characterized by a deficiency of functional Factor VIII (FVIII) leading to life-threatening bleeding in response to trauma and recurrent bleeding into soft tissue and joints. It is caused by any of a variety of mutations of the coagulation F8 gene, including missense or nonsense mutations, gene deletions, inversions, and splice junction mutations.

The worldwide prevalence of hemophilia A is estimated to be 17.1 cases per 100,000 males and worldwide incidence is approximately 1 in 5000 male births.[1,2] Hemophilia A is expected to be equally distributed across the world.[3,4] Approximately 165,000 diagnosed cases of hemophilia A are known to the World Federation of Hemophilia (WFH), but it is estimated that the majority of individuals with hemophilia in the developing world (>75%) remain undiagnosed.[3,4]

The current number of males with hemophilia living in the United States is estimated to be between 30,000 and 33,000.[2,4]

The severity of disease is characterized by the endogenous level of FVIII measured in the plasma. Severe hemophilia A (<1% endogenous FVIII activity level, i.e., <1 IU/dL) accounts for approximately 30% to 50% of all cases of hemophilia A).[1,3,5]

Severe hemophilia is a life-long disease, characterized by both spontaneous and traumatic bleeding episodes, for which there is no available cure. These bleeding episodes have the potential to be life-threatening, are often painful, can lead to disabling comorbidities, and significantly affect the patient's quality of life. Common symptoms of this condition include excessive bleeds from superficial abrasions and shallow lacerations as well as intraarticular, intramuscular, and intracranial bleeds. Mild hemophiliacs (5-25% of normal concentration of active clotting factor) have few to no bleeding episodes in the absence of serious trauma and can often be managed with desmopressin; most mild and moderate hemophiliacs (1-5% of normal concentration of clotting factor) can be treated as needed during bleeding episodes (BE). Severe hemophiliacs (<1% of normal concentration of clotting factor) require regular

supplementation with exogenous FVIII (usually every 2-3 days) as well as additional prophylactic doses prior to surgical procedures and after trauma.

Per current WFH Guidelines for the Management of Hemophilia as well as national and international hemophilia organizations' recommendations, the standard of care for all patients with severe hemophilia is regular prophylactic therapy with FVIII replacement products or non-factor replacement products to prevent bleeding, starting early in life (before age 3) to prevent development of musculoskeletal complications from recurrent joint and muscle bleeds.[6]

3 PRODUCT INFORMATION

3.1 Product Description

Efanesoctocog alfa (proposed propriety name: ALTUVIIIO) is a fully recombinant fusion protein comprising a single chain B-domain deleted (BDD) analogue of human FVIII covalently fused to the Fc domain of human immunoglobulin G1 (IgG1), the FVIII-binding D'D3 domain of human von Willebrand factor (VWF), and 2 XTEN polypeptides. ALTUVIIIO contains 2829 amino acids with a molecular weight of 312 kDa. ALTUVIIIO is synthesized as 2 polypeptide chains which are covalently linked by 2 Fc hinge disulfide bonds. The Fc domain includes the hinge, CH_2, and CH_3 domains of IgG1. The Fc, VWF, and XTEN portions of the molecule extend the half-life of ALTUVIIIO in plasma.

ALTUVIIIO is produced by recombinant DNA technology in a human embryonic kidney (HEK) cell line, which has been extensively characterized. ALTUVIIIO is manufactured without addition of human- or animal-derived components and purified by a combination of multiple chromatography steps, a detergent viral inactivation step, a nano filtration step for viral clearance, and ultrafiltration steps.

ALTUVIIIO, Antihemophilic Factor (Recombinant), Fc-Von Willebrand Factor-XTEN Fusion Protein, is a sterile, non-pyrogenic, white to off-white lyophilized powder for reconstitution for intravenous injection. The product is supplied in single-dose vials containing nominal potencies of 250, 500, 750, 1000, 2000, 3000, or 4000 international units (IU). Each vial of ALTUVIIIO is labeled with the actual content in IU. The powder for injection is reconstituted with 3 mL sterile water for injection (sWFI) supplied in a sterile prefilled syringe. The reconstituted solution should be essentially free of particles. The final product contains the excipients: sucrose (5% w/v), calcium chloride dihydrate (5 mM), histidine (10 mM), arginine hydrochloride (250 mM) and polysorbate 80 (0.05% w/v).

3.2 Proposed Indication

The sponsor's proposed indication statement as submitted to the original BLA 125771/0 is: ALTUVIIIO is a long-acting recombinant antihemophilic factor (coagulation factor VIII)

with high sustained FVIII activity indicated in adults and children with hemophilia A (congenital factor VIII deficiency) for:

- Routine prophylaxis to reduce the frequency of bleeding episodes,
- On demand treatment & control of bleeding episodes,
- Perioperative management of bleeding.

OBPV defers to product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

4 PERTINENT REGULATORY HISTORY

ALTUVIIIO is not licensed in the United States or elsewhere.

5 DESCRIPTION OF ALTUVIIIO CLINICAL TRIAL SAFETY DATABASE

5.1 Clinical studies

The sponsor submitted safety data from three Phase 3 studies in support of the indication: one completed study and two ongoing studies. The Summary of Clinical Safety (SCS) data cut-off date for the 2 ongoing studies was January 24, 2022. The sponsor also submitted data from 3 additional Phase 1 studies that will not be labeled and will not be reviewed in this memorandum.

Tabular summaries of the 3 Phase 3 studies are provided in Table 1.

Table 1. Summary of clinical studies supporting the safety of ALTUVIIIO

Study	N	Description	Status
EFC16293: (XTEND-1)	159 (133 in Arm A; 26 in Arm B)	Open-label multicenter study to assess the safety, efficacy, and pharmacokinetics (PK) of ALTUVIIIO in Previously Treated Patients (PTPs) with severe hemophilia A, ≥12 years of age.	Completed
EFC16295: (XTEND-kids)	Planned: N=65	Open-label study to assess the safety,	Ongoing

	Enrolled as of the cut-off date: N= 67 (31 in the <6 years of age cohort and 36 in the 6 to <12 years of age cohort).	efficacy, and PK of ALTUVIIIO in pediatric PTPs with severe hemophilia A, <12 years of age.	
LTS16294: (XTEND-ed)	Planned: N=262 (215 in Arm A who roll over from EFC16293); 37 Chinese participants in Arm B; up to 10 major surgery participants in Arm C). Enrolled as of the cut-off date: N= 159 (123 in Arm A; 32 in Arm B; 4 in Arm C).	Open-label study to assess the long-term safety and efficacy of ALTUVIIIO in PTPs with severe hemophilia A. In addition, 2 separate open-label arms with PTPs newly initiated on ALTUVIIIO in China; and PTPs who are planned to undergo major surgery.	Ongoing

*Adapted from Table 1 of BLA 125771/0, Module 2.7.4, Summary of Clinical Safety (SCS)

5.2 Review of clinical safety data

As of the data cut-off date of January 24, 2022, across the three Phase 3 clinical studies (EFC16293, EFC16295, and LTS16294), a total of 262 unique participants received at least one dose of ALTUVIIIO (safety analysis set). Of the 262 participants, the numbers of participants per age category were: 31 <6 years; 36 aged 6 to <12 years; 37 aged 12 to 17 years; 152 aged 18 to 64 years; and 6 ≥ 65 years (SCS pg. 134, Table 15).

The sponsor considered the following adverse events (AEs) as adverse events of special interest (AESIs):

- Symptomatic overdose (serious or nonserious) with ALTUVIIIO or placebo
  - An overdose (accidental or intentional) is an event suspected by the Investigator or spontaneously notified by the participant and defined as any dose of study treatment administered to a participant or taken by a participant that exceeds the dose assigned to the participant according to the protocol
- Development of a FVIII inhibitor
- Grade 3 or higher allergic reactions per Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (see below), or an anaphylactic reaction in association with ALTUVIIIO administration.
  - Grade 3 allergic reaction: bronchospasm or hospitalization indicated for clinical sequelae or intravenous intervention indicated,
  - Grade 4 allergic reaction: Life-threatening consequences or urgent intervention indicated,
  - Grade 5 allergic reaction: Death.
- An embolic or thrombotic event, except for injection site thrombophlebitis

In addition to potential development of neutralizing antibodies (inhibitors) to FVIII, use of this product may induce immunogenicity in the form of both non-inhibitory anti-drug antibodies (ADAs) and novel antibodies to human embryonic kidney proteins. This reviewer considered treatment-emergent (either treatment-boosted or treatment-induced) non-inhibitory ADAs against ALTUVIIIO as an AESI.

5.2.1 Clinical study EFC16293

Study EFC16293 was a Phase 3, open-label, multinational, multicenter study of the safety, efficacy, and pharmacokinetics (PK) of IV ALTUVIIIO in PTPs ≥12 years of age with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe hemophilia A). A total of approximately 150 participants were planned to be enrolled and treated with ALTUVIIIO.

To evaluate the safety and tolerability of ALUTVIIIO, the following were the safety endpoints of EFC16293:

- Development of Factor VIII inhibitors
- Occurrence of AEs and serious adverse events (SAEs)
- Clinically significant changes in physical examination, vital signs, and laboratory tests
- Occurrence of thrombotic or embolic events

For this study, pregnancy of a female participant as well as pregnancy occurring in a female partner of a male participant was considered an AESI.

All 159 participants included in the study received at least one dose of ALTUVIIIO. Of the 159 evaluated participants, 134 (84.3%) were adults (18 years of age and older) and

25 (15.7%) were adolescents (12 to <18 years of age). One female participant was enrolled; all the other participants were male. Race was reported as Asian in 29 participants, Black in 3 participants, White in 97 participants, and Other in 4 participants. Race was not reported in 26 participants. There were 152 (95.6%) participants treated for at least 39 weeks and 98 (61.6%) participants treated for at least 52 weeks.

AEs:
Of the 159 participants who received at least one dose of ALTUVIIIO, 123 participants (77.4%) had at least one AE, with a total of 394 AEs reported.
The most frequently reported (>3% of participants overall) AEs were headache (32 [20.1%] participants), arthralgia (26 [16.4%] participants), fall (10 [6.3%] participants), back pain (9 [5.7%] participants), COVID-19 and fatigue (7 [4.4%] participants each), contusion, haemophilic arthropathy, and nasopharyngitis (6 [3.8%] participants each), and joint injury, pain in extremity and toothache (5 [3.1%] participants each) (SCS pg. 58 – 59).
The AEs identified as related to the product by investigators were headache, arthralgia, and back pain. All events were assessed by the Investigator as non-serious and none resulted in discontinuation of ALTUVIIIO (SCS pg. 61 – 61).

Serious Adverse Events (SAEs): There were 18 SAEs. Two system organ class (SOC) included more than 2 events - 4 events (2.5%) were classified in Musculoskeletal and Connective Tissue Disorders and 3 (1.9%) in Nervous System Disorders SOC (Table 16.2.7.13 of EFC16293 16.2.7; Adverse event data in Module 5.3.5.1 Appendices 16.2). The majority of SAEs were assessed by the Investigator as mild to moderate in severity and not related to ALTUVIIIO. One SAE of CD4 lymphocytes decreased in a participant with a history of HIV was assessed by the Investigator as related to ALTUVIIIO and resulted in discontinuation of study drug. Another SAE of combined tibia-fibula fracture also resulted in discontinuation of study drug due to use of another FVIII product (prohibited medication) (SCS pg. 63 – 64).

Deaths: There was 1 death due to metastatic pancreatic carcinoma with multiple nodules of the liver.

AESIs: There were no cases of inhibitor development to FVIII, and there were no reports of Grade 3 or higher allergic reaction, anaphylaxis, or vascular thrombotic events.

Four participants had treatment-emergent ADAs. The ADA response for all 4 participants was transient and lasted less than 16 weeks. One participant reported AEs (arthralgia, red blood cell increased, rhinitis allergic and COVID-19 pneumonia) during the time when they possibly had a positive ADA result. Two participants did not have AEs concurrent with positive ADA results. The 4th participant did not have an AEs reported during the study.

There were 9 non-serious potential hypersensitivity reactions identified in 6 participants. These were skin rash due to intravenous (IV) morphine, infusion site skin rash, injection

site dermatitis (2 events), papular urticaria in bilateral lower extremities, medical device site rash, allergic dermatitis, wrist rash and angioedema (SCS pg. 66).

There are no narratives available for 2 participants who had these reactions: medical device skin rash and allergic dermatitis. Narratives for the other 4 participants who experienced possible hypersensitivity reactions are summarized below (Module 1.11.3, Response to FDA Request dated 08-Dec-2022):

- Subject (b) (6), Infusion site skin rash: 56-year-old male study participant received ALTUVIIIO on study day 127 for a planned revision surgery of left total knee replacement. On the same day, an AE of rash attributed to IV morphine (received in context of planned surgery) was reported. Rash resolved on day 128. On day 129, study participant received ALTUVIIIO as prophylaxis following the surgery. On the same day, a skin rash after removal of the infusion-needle developed and the AE of infusion site rash was reported. The rash resolved on day 130. No action was taken ALTUVIIIO for both events of rash. The investigator assessed that both events were not related to ALTUVIIIO or the study procedures. The study participant continued to received treatment with ALTUVIIIO and continued to enroll in the long-term study LTS6294.

- Subject (b) (6), Injection site dermatitis: 30-year-old male study participant received ALTUVIIIO on study day 1. On the same day, an AE of injection site dermatitis was reported which resolved on the same day. The study participant received ALTUVIIIO on day 15 and an AE of injection site dermatitis was reported. The rash resolved on the same day. No action was taken with ALTUVIIIO. The investigator assessed both events of mild contact dermatitis at injection site as related to ALTUVIIIO or study procedures. Of note, this participant also experienced an AE of “papular urticaria of bilateral lower extremities;” no narrative for this AE was submitted by the sponsor.

- Subject (b) (6), Wrist rash: 14-year-old male study participant received ALTUVIIIO on day 1. On day 10, an AE of wrist rash was reported, which resolved on day 11. No action was taken with ALTUVIIIO. The investigator assessed that the mild event of wrist rash as not related to ALTUVIIIO or study procedures. No additional information about the event or about the reasoning for investigator’s relatedness assessment was provided.

- Subject (b) (6), Angioedema: 14-year-old male study participant received ALTUVIIIO on study day 1 and on study day 57. On day 81, study participant reported upper lip angioedema which resolved in day 83. The investigator assessed the event was not related to ALTUVIIIO or the study procedure.

Two pregnancies in female partners of male participants, 1 in each arm, were reported during the study. One female partner of a participant delivered a healthy baby at term,

without labor and delivery complications, congenital anomalies, or birth defects. Pregnancy of the 2nd participant's female partner was still ongoing at the time of the report.

There were no reports of symptomatic overdoses during the study.

Reviewer comment**:** *The investigator identified alternative etiologies for 4 possible hypersensitivity reactions: morphine, actigraph device, and contact dermatitis (2 events). For the remaining 5 reactions, investigator's assessment was that these were unrelated to ALTUVIIIO or study procedures. There was no action taken and all events were reported as recovered or resolved.*

Actigraph device and contact dermatitis are reasonable alternate causes. However, for participant (b) (6) *, cause cannot be attributed to morphine alone. While the first rash may be due to IV morphine, the participant experienced a second rash following surgery when he did not receive IV morphine. Thus, the rashes may be due to ALTUVIIIO or contact dermatitis. It is also notable that participant* (b) (6) *also experienced "papular urticaria bilateral lower extremities" in addition to injection site dermatitis, which may also be a manifestation of hypersensitivity. No additional details are available and causal relationship to ALTUVIIIO for this event is unclear. The cause of wrist rash for participant* (b) (6) *is unclear. The angioedema experienced by participant* (b) (6) *is unlikely related to ALTUVIIIO because timing is medically unreasonable. Angioedema developed too long after the last ALTUVIIIO dose. There are no details available regarding the participant who reported allergic dermatitis, therefore a causal relationship cannot be determined.*

The assessment of this reviewer is that 3 hypersensitivity events have reasonable alternate causes. For the remaining 6 events, cause is unclear and relationship to ALTUVIIIO cannot be ruled out. Of note, the proposed label includes a Warning for hypersensitivity reactions (section 5*).*

Otherwise, no AE patterns or clusters were noted that were suggestive of safety concerns.

5.2.2 Clinical study EFC16295

Study EFC16295 is a multinational, multicenter, single-arm, open-label Phase 3 study of the safety, efficacy, and pharmacokinetics (PK) of IV administered ALTUVIIIO in PTPs <12 years of age with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe hemophilia A). The study is comprised of 2 age cohorts of children (<6 years and 6 to <12 years), and participants were to receive ALTUVIIIO at a dose of 50 IU/kg IV once weekly for 52 weeks. Approximately 65 participants were planned to be enrolled to achieve at least 50 participants (25 participants <6 years of age and 25 participants 6 to <12 years of age) completing approximately 52 weeks of treatment to obtain at least 50 exposure days

(EDs). After completion of the study, participants are invited to enroll in an open-label extension study (LTS16294).

The primary objective of Study EFC16295 is to evaluate the safety of ALTUVIIIO in pediatric PTPs with hemophilia A. The primary endpoint is the occurrence of FVIII inhibitor development.

All participants are male. The mean duration of ALTUVIIIO dosing was 36.53 weeks. As of the SCS data cut-off date, all 67 enrolled participants had been exposed to at least 1 dose of ALTUVIIIO. The sponsor submitted a 120-day safety update for this study, with cut-off date of June 30, 2022 (BLA 125771/0, Module 5.3.5.3 ISS 120 Day Safety update). There were 7 additional participants (all in the <6 years of age cohort) compared to the initial submission. The review that follows will include data from the 120-day safety update.

AEs: Of the 74 participants who received at least one dose of ALTUVIIIO, 55 (74.3%) had at least one AE, with a total of 188 AEs reported. The most frequently reported AEs (>5% of participants overall) were SARS-CoV-2 test positive (12 [16.2%] participants), upper respiratory tract infection (8 [10.8%] participants), pyrexia (7 [9.5%] participants), asymptomatic COVID-19 (6 [8.1%] participants), gastroenteritis viral and nasopharyngitis (5 [6.8%] participants each), and constipation, viral upper respiratory tract infection, and vomiting (4 [5.4%] participants each).

Two participants experienced 5 AEs that were assessed by investigator as related to ALTUVIIIO, both in the <6 age cohort. The related AEs included alanine aminotransferase increased, aspartate aminotransferase increased, Von Willebrand's factor antigen increased and pyrexia in one participant; these AEs were classified as non-serious and mild in severity. The 5th related AE is in a participant that had increased coagulation FVIII level. This event was classified as non-serious and mild. No action was taken for the related AEs and outcome was reported as recovered or resolved (120-day safety update pg. 19-20). .

SAEs: Two participants experienced a total of 2 SAEs, both in the <6 years of age cohort. The reported SAEs included vascular device infection and dehydration. The participant with vascular device infection had experienced recurrent AEs of fever and rigors prior to confirmation of vascular device infection. The participant with dehydration presented to the hospital with closed head injury after being pushed by his sibling. Both events were assessed by the investigator as mild in severity and not related to ALTUVIIIO.

Deaths: There were no deaths.

AESIs: No cases of inhibitor development to FVIII were reported and there were no reports of Grade 3 or higher allergic reaction, anaphylaxis, or vascular thrombotic events. There were no treatment emergent ADAs.

An event of urticaria was reported in a 2-year-old participant ((b) (6)) who had been receiving weekly dosing of ALTUVIIIO for 3 months. The subject experienced "hives around eyes, mouth, face, and chest" despite no prior history of allergies. The event occurred 3 days after a regular weekly dose, and the participant was treated with 2 doses of intramuscular epinephrine, oral dexamethasone, and oral cetirizine with resolution. The etiology of the event was reported as unknown. The Investigator assessed the event as non-serious and not related to ALTUVIIIO. There was no action taken with ALTUVIIIO and no report of recurrence on continued ALTUVIIIO treatment (SCS pg. 93).

There were no reports of symptomatic overdoses during the study.

Reviewer comment: *The SAEs of vascular device infection and dehydration are likely not related to ALTUVIIIO. The infection was due to the vascular device. Dehydration was likely related to closed head injury. The event of urticaria is unlikely related to ALTUVIIIO because of timing. Hives caused by an allergic reaction usually occur minutes to 2 hours of exposure to the culprit allergen. The hives occurred 3 days after the last weekly ALTUVIIIO dose.*

Otherwise, no AE patterns or clusters were noted that were suggestive of safety concerns.

5.2.3 Clinical study LTS16294

LTS16294 (XTEND-ed) is a Phase 3 open-label, multicenter study which is ongoing. The primary objective of Study LTS16294 is to evaluate the long-term safety of ALTUVIIIO in PTPs with hemophilia A. The primary endpoint associated with this objective is the evaluation of the occurrence of FVIII inhibitor development. A secondary objective is the assessment of safety and tolerability of ALTUVIIIO treatment. This study aims to supplement ALTUVIIIO clinical data by the inclusion of 2 cohorts of PTPs newly initiated on ALTUVIIIO: Chinese PTPs (in China; Arm B), and global PTPs who are planned to undergo major surgery (Arm C).
The study comprises 3 arms:

- **Arm A:** Participants who have completed Study EFC16293, Study EFC16295, any other potential ALTUVIIIO study, and participants who have completed Arm B or Arm C of this study (LTS16294) and roll over into Arm A. Participants in Arm A continue receiving ALTUVIIIO prophylaxis treatment at a dose of 50 IU/kg IV once-weekly for a cumulative total of 100 EDs from the parent study and/or Study LTS16294. Participants are offered the opportunity to continue in this study for up to 4 years, unless ALTUVIIIO is commercially available in their applicable participating country.
- **Arm B:** Chinese PTPs of any age who are newly initiated on ALTUVIIIO prophylaxis treatment at a dose of 50 IU/kg IV once-weekly for 52 weeks. After 52 weeks of treatment in Arm B, participants are able to roll over into

Arm A. Enrollment of children <12 years of age opened after sufficient exposure in adults and adolescents enrolled in this arm.

- **Arm C:** PTPs of any age who are newly initiated on ALTUVIIIO prophylaxis treatment at a dose of 50 IU/kg IV once-weekly and undergo planned major surgery after at least 6 initial EDs with ALTUVIIIO, within 26 weeks from Day 1. After 52 weeks of treatment in Arm C, participants are able to roll over into Arm A. Enrollment in Arm C opened after completion of enrollment in the parent studies EFC16293 (adult/adolescent) and EFC16295 (pediatric).

The sponsor submitted a 120-day safety update for this study with a cut-off date of June 30, 2022. There were 59 additional participants. The following summary is inclusive of data from both the SCS and 120-day safety update.

Arm A

As of the data cut-off date, Arm A comprised 176 participants who had completed a prior ALTUVIIIO study and received at least 1 dose of ALTUVIIIO in Study LTS16294. The mean age of the participants was 33.8 years (range: 4 to 74 years); 18 participants were <12 years of age, 26 participants were between 12 and 17 years, 127 participants were between 18 and 64 years, and 5 participants were ≥65 years. Of the 176 participants, 175 (99.4%) were males and 1 (0.6%) was a female. With respect to race, 116 (65.9%) participants were white, 38 (21.6%) participants were Asian, 4 (2.3%) participants were Black or African American; race was not reported for 14 (8.0%) participants. The mean duration of ALTUVIIIO dosing was 30.68 weeks; 99 (86.8%) participants had at least 4 weeks of exposure, 68 (59.6%) participants had 13 weeks of exposure, and 18 (15.8%) participants had at least 26 weeks of exposure.

AEs: Of the 176 participants in Arm A, 79 (44.9%) participants experienced a total of 224 AEs. The most frequently (≥3 participants overall) reported AEs were COVID-19 (15 [8.5%] participants), headache and nasopharyngitis (8 [4.5%] participants, each), and asymptomatic COVID-19 and arthralgia (6 [3.4%] participants, each).
One participant experienced a nonserious AE of facial paralysis that was assessed by the Investigator as related to ALTUVIIIO. The rationale provided was that there was “no event more likely than the administration of the study drug.” The ALTUVIIIO doses was not changed, and outcome was reported as recovered or resolved (120-day safety update pg. 32).

SAEs: In Arm A, there were 17 SAEs in 12 participants. Reported SAEs included femur fracture (2 events in 2 participants), periprosthetic fracture (2 events in 1 participant), meningitis viral, pericoronitis, cerebral infarction, status epilepticus, deep vein thrombosis (DVT), chronic obstructive pulmonary disease, nasal obstruction, arthropathy, haemophilic arthropathy, osteoarthritis, synovitis, fall, and wrist fracture. The participant ((b) (6)) who suffered a fall, femur fracture and wrist fracture discontinued treatment. The participant with DVT ((b) (6)) subsequently withdrew from the study. DVT and cerebral infarction events were also classified as AESIs, with more details below.

Deaths: There were no deaths.

AESIs: Inhibitor development to FVIII was not detected and there were no reports of serious allergic reactions or anaphylaxis. ADA results were not reported.

Two participants experienced events of thrombosis, described below:

- Study (b) (6), DVT: 32-year-old male participant with a medical history of hemophilic osteoarthropathy (bilateral elbows, knees, and ankles) and positive hepatitis C antibody enrolled in Arm A. Five days after a dose of ALTUVIIIO, the participant sustained a left distal femur fracture following a fall while skiing. He had no access to ALTUVIIIO and was treated with Novoeight. He underwent surgical correction of the left distal femur fracture without significant complications. Two days after surgery, a lower extremity ultrasound was performed which revealed an occlusive left lower extremity deep vein thrombosis. Lovenox was started. The Investigator assessed the event of deep vein thrombosis as not related to ALTUVIIIO and recovering or resolving. The action taken with ALTUVIIIO was reported as drug infusion interrupted or delayed. The participant was subsequently withdrawn from the study due to the use of prohibited medications (Novoeight and Lovenox) (SCS pg. 104; Module 5.3.5.3 Integrated Summary of Safety (ISS) Appendix 4, Section 1.7).
- Study (b) (6), cerebral infarction: 62-year-old male participant with a past medical history significant for chronic atrial fibrillation, dyslipidemia, and HIV infection. Prior hemophilia treatment consisted of turoctocog alfa, as needed. He was not treated with anticoagulant or antiplatelet medication for atrial fibrillation. One day after receiving an on-demand dose of ALTUVIIIO (for spontaneous bleed), he was found on the floor, unable to ambulate and with facial asymmetry. This occurred six days after a routine dose of ALTUVIIO. He subsequently lost movement and sensation on half of his body. Computed tomography angiography revealed cerebral infarction of the right middle cerebral artery. He was treated with thrombectomy. Low molecular weight heparin was initiated. Within 1 week, participant had total recovery of signs and symptoms. The investigator's causality assessment was not related (120-day safety update pg. 4-5).

There were no reports of symptomatic overdoses in this Arm.

Reviewer comment: *DVT is unlikely related to ALTUVIIIO. Participant suffered a traumatic femur fracture. He underwent surgery and was treated with another Factor VIII product prior to surgery. DVT developed after surgery. DVT is likely related to traumatic orthopedic injury and surgery. Cerebral infarction is unlikely related to ALTUVIIIO. Participant's history of untreated atrial fibrillation is a strong risk factor for thrombosis.*

Otherwise, no AE patterns or clusters were noted that were suggestive of safety concerns.

Arm B

Arm B had 37 participants. All participants were males. All participants except 1 for whom race was not reported were Asian. The mean duration of dosing was 41.82 weeks, of which 37 (100 %) participants had at least 4 weeks of exposure.

AEs: Of the 37 participants in Arm B, 21 (56%) participants experienced a total of 43 AEs. No AEs led to treatment discontinuation or death. The most frequently (>3% of participants overall) reported TEAEs were nasopharyngitis(4 [10.8%] participants), upper respiratory tract infection (3 [8.1%] participants), and joint injury, paronychia, and pyrexia (2 [5.4%] participants each).These AEs were assessed by the Investigator as mild in severity and not related to ALTUVIIIO.

SAEs: In Arm B, there were 6 SAEs in 3 participants: skin infection and thermal burn in the same participant, thrombosis, hemangioma, and pain in a second participant, and joint injury in a third participant. . The events of skin infection, thermal burn and joint injury were classified by the investigator as unrelated to ALTUVIIO. The thrombosis event was also classified as AESIs, with details described below. There was no action taken for any of the SAEs. The outcomes were reported as recovered/resolved.

Deaths: There were no deaths.

AESIs: There were no cases of inhibitor development to FVIII and there were no reports of serious allergic reactions or anaphylaxis. ADA results were not reported.

One participant with a history of right-hand hemangioma experienced 2 events of thrombosis (1 non-serious, 1 serious) involving the hemangioma with onset 3 days after the first injection of ALTUVIIIO. The same participant experienced a third event of thrombosis during a major/surgical rehabilitation period.

- Subject (b) (6), Thrombosis: 13-year-old male participant with a medical history of a right palm hemangioma since 2013 and hemophilic arthropathy enrolled in Arm B. Three days after the first dose of ALTUVIIIO, he was admitted to the Department of Orthopedics at the study site because of a mass below the metacarpophalangeal joint of the ring finger of the palm; timing of onset of symptoms was unclear. An ultrasound revealed “hemangioma of the right hand with partial thrombosis on the back of the hand.” The subject was subsequently documented as experiencing 2 additional events of thrombosis at the same site on the back of the right hand; the degree of resolution of the thrombosis between the documented events was unclear from the narrative. The investigator assessed the first two events as related to the product, but as the third event occurred approximately 3.5 months after surgery to remove the hemangioma, the investigator assessed the event as attributable to the high thrombotic risk related to the post-surgical period and as not related to ALTUVIIIO. There was no action taken with ALTUVIIIO. The participant was subsequently withdrawn from the

study due to violation of eligibility criteria as a history of inhibitor development to FVIII prior to enrollment in Study LTS16294 was identified (SCS pg. 106; Module 5.3.5 ISS Appendix 4, Sections 1.16 and 1.21.1).

There were no reports of symptomatic overdoses in this Arm.

Reviewer comment: *The participant has history of hemangioma and arthropathy and is at risk for thrombotic events. The clinical course with respect to development and resolution of the thrombi is unclear from the provided narrative, and it is possible that these existed prior to ALTUVIIIO treatment and were therefore unrelated. However, he had no known prior history of thrombosis. Therefore, the assessment of this reviewer is that the events are of unclear relatedness to the product.*

Otherwise, no AE patterns or clusters were noted that were suggestive of safety concerns.

Arm C
In Arm C, there were 5 male participants enrolled. All participants were white males. The duration of ALTUVIIIO dosing ranged from 6.37 to 40.20 weeks.

Of the 5 participants, 4 participants experienced a total of 15 AEs including headache (4 AEs), nasopharyngitis (2 AEs), arthralgia (2 AEs), back pain, intervertebral disc protrusion, procedural nausea, tooth impacted, SARS-CoV-2 test positive, neck pain, and gingival hypertrophy. None of these events were considered to be related to ALTUVIIIO or assessed by the Investigator as severe.

SAE: One participant experienced an SAE of tooth infection. This event was assessed as not related to ALTUVIIIO.

No deaths or AESIs have been reported (SCS pg. 107,120-day safety update). ADA results were not reported.

6 SPONSOR'S PHARMACOVIGILANCE PLAN

Table 2. Sponsor's Pharmacovigilance Plan

Type of Concern	Safety Concern	Proposed Action
Important Identified Risk	None	None
Important Potential Risk	Inhibitor development to Factor VIII	Routine Risk Mitigation Measures: Labelling USPI Sections 5, 5.2, 5.3 and 17 Routine Pharmacovigilance Activities: Standard Individual Case Safety Report (ICSR) reporting, Signal detection and specific follow-up questionnaire for inhibitor development

		Additional Pharmacovigilance activities: Completion of clinical studies (under IND) of pediatric patients with Hemophilia A (EFC16295) and long-term extension study in PTPs (LTS16294); observational registry in Previously Untreated Patients (PUPs)
Missing	Use in PUPs	Routine Risk Mitigation Measures: Labelling in USPI Sections 5, 5.2 Routine Pharmacovigilance activities: Standard ICSR reporting, aggregate reporting, and signal detection Additional Pharmacovigilance Activities: Observational registry study in PUPs

*Adapted from Table 3 of STN125771/0, Module 1.16.1, Risk Management Plan

6.1 Safety-related Post-marketing Study

The sponsor plans an Observational Registry Study in PUPs which will be conducted as a voluntary study. This study is being executed as an externally sponsored collaboration with the American Thrombosis and Hemostasis Network (ATHN) (Study Sponsor). The final protocol is anticipated to be submitted to the FDA by March 31, 2023. The draft study protocol synopsis for the prospective, observational, multicenter registry study of efanesoctocog alfa in Previously Untreated Patients (PUPs) is described below:

Protocol Title: Safety and Effectiveness of Efanesoctocog alfa in Previously Untreated People (PUP) with Hemophilia A: A Module of the PUPs Arm of the Hemophilia Cohort of ATHN Transcends Prospective Observational Study

Study objectives: To describe the safety, tolerability, and effectiveness of efanesoctocog alfa in PUPs with hemophilia A

Study endpoints:
Primary endpoints

- Occurrence of FVIII inhibitor development as measured by the (b) (4) Bethesda Assay. Inhibitor testing to be performed at a central lab.
- Occurrence of any European Haemophilia Safety Surveillance project endpoint.
  - Allergic or other acute events
  - Treatment-emergent side effects of therapy
  - Transfusion transmitted infection
  - Thrombosis/embolism
  - Cardiovascular events

    - Malignancies
    - Neurological events
    - Death
- Occurrence of any of the following adverse events of special interest:
    - Injection site reactions
    - Drug-induced liver injury
    - Severe, unanticipated bleeding
    - Hospitalizations
    - Pregnancy
    - Overdose

Study design: A prospective, observational, open-label, single arm, multicenter study evaluating the safety, tolerability, and effectiveness of efanesoctocog alfa in PUPs with Hemophilia A. The study will use the hemophilia cohort of the ATHN Transcends Study. Following confirmation of eligibility, a participant can be treated either on-demand or prophylactically with efanesoctocog alfa. The study will last for a total of 7 years. The study will end when at least 50 participants have attained 50 EDs. Surgery is allowed during the study. Immune tolerance induction with efanesoctocog alfa is allowed during the study for those participants developing a positive inhibitor after exposure to efanesoctocog alfa.

Study population: This study will be conducted in PUPs who are less than 18 years of age who are affected by severe HA (FVIII activity < 1%).

Statistical Methods: In general, all statistical analyses will be descriptive in nature. No formal comparison is planned. No hypothesis will be formally tested. Continuous variables will be summarized and presented by number of observations, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by the number and percentage in each category.

Final protocol submission: March 31, 2023
Study completion date: March 31, 2030
Final study report planned date: June 30, 2030

7 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

7.1 Important Identified Risks

As per the sponsor's assessment, there are no important identified risks for ALTUVIIIO.

7.2 Important Potential Risks

Inhibitor development to Factor VIII:

The sponsor lists inhibitor development to FVIII as an important potential risk. Development of inhibitors to FVIII is considered as the most significant treatment-related complication in patients with hemophilia A.[7] FVIII inhibitors are antibodies that neutralize the procoagulant activity of FVIII replacement therapy. As a result, the response to infused factor concentrate will be inadequate and the frequency and/or severity of bleeding events may be increased. The Sponsor intends to develop a specific adverse reaction follow-up questionnaire for documenting inhibitor development to FVIII. Per the sponsor, routine risk mitigation measures are sufficient to mitigate the risk of inhibitor development to FVIII and additional measures are not necessary. DPV agrees that routine pharmacovigilance (PV) is adequate.

Thromboembolic events (TEEs): Of note, the sponsor's PVP safety specifications do not include the risk of TEEs. However, OBPV/DPV has recommended the inclusion of TEEs as an important potential risk based on data from Study LTS16294, an ongoing, open-label extension study to evaluate long-term safety of clinical trial participants. Study LTS16294 reported 3 participants with vascular thrombosis; of whom one subject experienced product-related TEEs as per investigator assessment. This participant (Subject (b) (6)) experienced 3 thrombotic events, of which 2 thrombotic events occurred 3 days following administration of ALTUVIIIO and were assessed by the investigator to be related to ALTUVIIIO (please see additional details in section 5.2.3 of memorandum). On November 2, 2022, OBPV/DPV sent an information request (IR) to the sponsor recommending inclusion of TEEs in the PVP as an important potential risk. The sponsor concluded that addition of TEEs to the PVP is not warranted (Module 1.11.3 Response to FDA Request dated 02-Nov-2022-PV). OBPV/DPV sent an IR on January 18, 2022, to ask for clarification of the sponsor's assessment of these TEE events. In their response, the sponsor stated that all 3 study participants had underlying risk factors for thrombosis. While the investigator assessed 2 events occurring in participant (b) (6) as product-related AEs, it is Sanofi's position that all the events of thrombosis described in the 3 participants are primarily related to underlying risk factors for thrombosis and that these events are not related to ALTUVIIIO (Module 1.11.3 Response to FDA Request dated 18-Jan-2023-Clinical DPV). OBPV/DPV's recommendation continues to be to include TEE as a safety specification in the PVP, given the uncertainty of relatedness of at least two events of thrombosis. Should the product be approved, OBPV/DPV will require enhanced pharmacovigilance with sponsor submission of all TEE reports (regardless of seriousness) as expedited (15-day) reports to FAERS, and an assessment of TEEs in periodic safety reports. Enhanced pharmacovigilance will continue for 3 years post-licensure. As OBPV/DPV reviews ongoing safety surveillance data, changes may be made to update the PVP, as we gain postmarketing experience with this product and when the ongoing Study LTS16294 is completed. Note that the risk of TEEs was discussed with the clinical reviewer.

Hypersensitivity reactions: A potential risk with FVIII therapy, not included in the sponsor-proposed PVP is hypersensitivity reactions. The clinical trial data included events which could not be ruled out as possibly product-related hypersensitivity reactions. Allergic reactions with FVIII therapy occur in <1% of patients with

hemophilia.[8] Historically, allergic reactions were more commonly seen when treatment with FVIII replacement was based on cryoprecipitate and low-purity plasma-derived FVIII concentrate.[8] In an IR sent November 9, 2022, OBPV/DPV recommended that hypersensitivity reactions be listed in the PVP. Per the sponsor, available safety data for ALTUVIIIO did not definitively reveal these AEs, so sponsor did not list this under "Important Potential Risks" (Module 1.11.3 Response to FDA Request dated 02-Nov-2022-PV). The sponsor has included "Hypersensitivity reactions" under Section 5 of ALTUVIIIO's proposed United States Prescribing Information (USPI). While OBPV/DPV continues to recommend that hypersensitivity reactions be included in the PVP given the uncertainty of relatedness of multiple possible hypersensitivity AEs observed during the trial, OBPV/DPV agrees that labeling and routine PV is reasonable risk mitigation, should the product be approved. As OBPV/DPV reviews ongoing safety surveillance data, changes may be made to update the PVP, as we gain postmarketing experience with this product.

Non-inhibitory ADAs: Another potential safety risk related to the product is immunogenicity in the form of non-inhibitory ADAs. The clinical significance of non-inhibitory ADAs is unknown at this time. Additionally, the fact that the positive ADA results were transient and only 1 subject to date have developed AEs concurrent with ADA positive results suggest that these AEs would rarely manifest. Exclusive use of PTPs in the clinical trials likely restricted study patients to individuals inherently less prone to immunogenicity. Acquiring additional data from ongoing trials, and routine PV are sufficient to monitor risks associated with these AEs.

7.3 Important Missing Information

Use in Previously Untreated Patients (PUPs)
The safety profile of ALTUVIIIO in PUPs is not yet known as this population was excluded from completed and ongoing clinical studies with ALTUVIIIO. However, the targeted population for the indication in children may include PUPs. As the incidence of inhibitor development to FVIII is higher in PUPs compared to PTPs (defined as having > 150 EDs to FVIII therapy), the use of ALTUVIIIO in PUPs is considered Missing Information. The safety profile in PUPs, including the risk of inhibitor development to FVIII, will be further described postapproval through a disease registry (see postmarketing study section above).

8 DPV ASSESSMENT

Available data shows ALTUVIIIO is well-tolerated with reported AEs consistent with the known safety profile of other products in the Factor VIII replacement therapies product class. To date, no subjects in the clinical trials developed inhibitors; but the sponsor acknowledges inhibitor formation is an important potential risk. Hypersensitivity reactions and TEEs are rare risks for Factor VIII and VWF products. The Phase 3 trials did not reveal Grade 3 or higher allergic reactions. However, study EFC16293 participants experienced possible hypersensitivity AEs for which alternate causes are

unknown and relationship to ALTUVIIIO cannot be ruled out. Additionally, Study LTS16294 revealed one participant with thromboses which were assessed by investigator as related to ALTUVIIIO. The sponsor does not include hypersensitivity reactions and TEE in their PVP (for additional details, please see sections 5.2.3 and 7.2 for the memorandum). At this time, OBPV/DPV agrees with routine PV and labeling for hypersensitivity reactions, and enhanced PV for TEEs. As OBPV/DPV reviews ongoing routine surveillance, we may suggest added measures as needed.

All study subjects in the clinical safety database are PTPs. There is no available data describing use of this product in PUPs. Information for use of ALTUVIIIO in PUPs will be available after the postmarketing voluntary study is completed.

9 DPV RECOMMENDATIONS

Should the product be approved for treatment of adults and adolescents with hemophilia A for: 1) Routine prophylaxis to reduce frequency of bleeding episodes; 2) on-demand treatment and control bleeding episodes, and 3) perioperative management of bleeding, the sponsor will conduct:

- Routine pharmacovigilance in accordance with 21 CFR 600.80, and
- Enhanced pharmacovigilance for thromboembolic events (TEEs), with expedited reporting of TEEs (regardless of seriousness) and provide sponsor assessment for TEEs, based on cumulative and interval safety data, in periodic safety reports. Enhanced pharmacovigilance will continue for 3 years post-licensure.
- The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related postmarketing requirement or commitment (PMR/PMC) study. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

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APPENDIX
Materials Reviewed

Table A1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
June 30, 2022	Bioverativ	STN125771/0	Module 1.16.1, Risk Management Plan
June 30, 2022	Bioverativ	STN125771/0	Module 2.7.4, Summary of Clinical Safety (SCS)
June 30, 2022	Bioverativ	STN125771/0	Module 5.3.5.1 EFC 16923 8.3.3.3 Participant narratives - Deaths
June 30, 2022	Bioverativ	STN125771/0	Module 5.3.5.1 Appendices 16.2 EFC16293 16.2.7 Adverse Event Data
June 30, 2022	Bioverativ	STN125771/0	Module 5.3.5.3 ISS Appendix 4 – LTS 16294 – Adverse event data
October 14, 2022	Bioverativ	STN125771/0	Module 5.3.5.3 ISS – 120 – Day Safety Update
November 14, 2022	Bioverativ	STN125771/0	Module 1.11.3 Response to FDA Request dated 02-Nov-2022-PV
December 23, 2022	Bioverativ	STN125771/0	Module 1.11.3 Response to FDA Request dated 08-Dec-2022-Clinical
January 20, 2023	Bioverativ	STN125771/0	Module 1.11.3 Response to FDA Request dated 18-Jan-2023-Clinical DPV